MINIREVIEW

Genetics of Arterial Prothrombotic Risk States

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Coronary artery disease is a leading cause of death worldwide and the largest killer of men and women in the United States. The pathophysiology of myocardial infarction is multifactorial, and numerous physiologic systems converge to dictate the formation of the two fundamental lesions, thrombosis and atherosclerosis. In this review we address genetic aspects of arterial thrombosis and the key thrombotic factors that have been associated with the increased risk for its development. Specifically, we consider components of coagulation, fibrinolysis, and platelet adhesive receptors, and we review the genetic epidemiology and *in vitro* laboratory data regarding their risk for the acute coronary syndromes. In combination with traditional risk factor assessment, in the near future these inherited markers can be used to manage patients with vascular disease through a better utilization of invasive or expensive diagnostic testing, as well as pharmacologic intervention.

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Coronary artery disease (CAD) is a leading cause of death worldwide and the largest killer of men and women in the United States (1). In the United States each year, approximately 1,100,000 people experience acute myocardial infarction (MI) and among these, there are 500,000 deaths. In addition to the substantial personal suffering, the medical costs of CAD are enormous, with an estimated cost of $118.2 billion in the year 2000. The pathophysiology of MI is multifactorial and formation of the two fundamental lesions, thrombosis and atherosclerosis, involves numerous physiologic systems, including hemostasis, blood pressure regulation, and cholesterol and carbohydrate metabolism. Many different genes dictate the regulation of these traits, but to date, no major gain-of-function mutations for arterial thrombosis have been identified. As with most common and complex diseases like diabetes, psychiatric disorders, etc., those genes involved in MI are believed to exert only modest effects on the clinical phenotype (2). We might expect only those genetic changes causing small prothrombotic tendencies to persist in the gene pool with anything beyond a rare frequency, especially when considering the importance of maintaining blood fluidity. However, the relatively small magnitude of the individual effects does not lessen their importance, considering that overall genetic component to arterial thrombosis has been estimated to range from 20% (3) to 80% (4).

The first clues regarding a genetic component to MI came from studies on relatives of patients who died from MI, where the incidence of MI in first-degree relatives was two to four times higher than first-degree relatives of healthy individuals (3, 5, 6). A positive family history of MI was shown to be an independent risk factor (7) and this genetic effect was greatest in relatives of patients having an MI at a young age (8). Twin studies are a particularly powerful approach to assessing the influence of heredity on any phenotype. In a large study of 21,004 twins, the risk of death from MI was significantly greater in 7,310 monozygotic than in 13,694 dizygotic twins, and this effect was lost at older ages. Berg (9) and Sorensen *et al.* (10) obtained similar results in twin studies. As mentioned above, estimates of the effects of inheritance on MI have ranged from 20% to 80%, but there is likely some overestimation when the variation in environmental factors among dizygotic pairs is greater than in monozygotic pairs. It is interesting to note that more often than not, when the genetic risk is examined by gender, it is greater in women than in men (11–13). Clearly, there is an important and substantial genetic component to myocardial infarction, but for the most part this

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appreciation has focused on atherosclerosis. Genetic variations believed to regulate lipid metabolism (14), blood pressure (15, 16), and insulin metabolism (17) have been reviewed elsewhere, but there is a paucity of information available on the burgeoning field of genetics and arterial thrombosis.

Over the past decade the central role of thrombosis in acute coronary ischemia has gained attention, and basic research in the past few years has begun to identify some of the genes and their variations that regulate thrombotic traits. In this review we will examine the known components involved with coronary thrombosis, and in particular the genetic polymorphisms associated with these components. The definition of polymorphism will be taken to mean a stable DNA sequence variations occurring in greater than 1% of the chromosomes in the population. Although the purpose of this review is to focus on the genetic effects on thrombosis, inflammation is intertwined with both atherosclerosis and thrombosis, and we have included some brief comments on this subject as well.

Arterial Thrombosis

The pathophysiology of thrombosis involves complex interactions between the endothelial surface, platelets, and several activated coagulation factors. This was first proposed by Rudolf Virchow in 1856 and is now known as Virchow's triad. The three major factors that determine this triad are changes in the vessel wall, changes in blood flow, and changes in the coagulability of blood (18). These factors all interact to form a localized mass.

In acute coronary occlusion, the thrombotic process begins with injured endothelium or denuded vascular surfaces. When arterial subendothelium is disrupted, von Willebrand factor molecules are rapidly localized to the exposed collagen, and the initial platelet contact with the wound is a tethering to this insoluble form of von Willebrand factor via GPIbaα of the GPIb-IX complex (19). The tethering and rolling of platelets on the vessel wall can cause platelet activation and can up-regulate platelet GPIIb-IIIa and $\alpha_2\beta_1$ function. Stable adhesion and platelet activation is then mediated through integrin $\alpha_2\beta_1$ (platelet GPIa-IIa) binding to exposed collagen and platelet GPIIb-IIIa binding to von Willebrand factor and fibrinogen (20). Once platelets are activated, the GPIIb-IIIa receptor (which is the sole receptor responsible for platelet aggregation) undergoes a conformational change to a high-affinity ligand-binding state (21). Platelets then adhere to one another via fluid phase fibrinogen or vWf bridging to GPIIb-IIIa receptors, and an expanding thrombus ensues. During this phase of platelet activation coagulation is initiated by the exposure of the various blood elements to tissue factor in the vessel wall, thereby activating several coagulation factors and leading to the production of thrombin. In addition, platelet activation leads to the formation of phospholipid-rich microvesicles that enhances the conversion of prothrombin to thrombin. Thrombin itself is a potent platelet activator and contributes to stabilization of the arterial thrombus (22).

Fibrinogen

Fibrinogen plays a major role in the thrombotic process. It is integral to platelet aggregation, has direct effects on the vascular wall, has a direct influence on blood viscosity, and is an acute phase reactant (23). Fibrinogen is made up of three pairs of polypeptide chains, namely Aα, Bβ, and γ found on the long arm of chromosome 4 (23). Elevated plasma fibrinogen levels are strongly associated with the risk for MI, as initially reported in men (24, 25) and later in women (26, 27). In fact, the association with MI was stronger than for cholesterol, such that for each 1 standard deviation elevation in fibrinogen or cholesterol (24), the 5-year risk of an ischemic event was raised by 84% or 43%, respectively. The conclusions from these original studies have been supported in several meta-analyses (28, 29). Plasma fibrinogen levels are regulated in part by genetic effects, and Humphries *et al.* (30) have shown that some degree of this regulation occurs at the fibrinogen locus on chromosome 4, which harbors the three genes encoding the three fibrinogen subunits, Aα, Bβ, and γ. There is linkage disequilibrium across five polymorphisms scattered among these three genes (31), so studying one polymorphism is, in effect, like studying the others. However, it is important to note that nongenetic factors like cigarette smoking (32) appear to have a much greater effect on plasma fibrinogen levels than any of these fibrinogen gene polymorphisms. Most (33–36) but not all (37), studies have found an association between MI and fibrinogen polymorphisms.

Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1 is a major regulator of the fibrinolytic system. An increased plasma level of PAI-1 results in less plasmin degradation of fibrin, and thus, would be expected to be prothrombotic. PAI-1 levels are regulated by genetic and environmental factors. The regulation of PAI-1 expression through the 4G/5G polymorphism is modified by plasma triglycerides levels (38) and perhaps insulin as well (39). In addition, the sequence length polymorphism (4G/5G) in the promoter region of the PAI-1 gene identified by Dawson *et al.* (40) contributes to PAI-1 expression since individuals with the 4G/4G genotype have 25% higher PAI-1 levels than those with the 5G/5G genotype (41).

Reduced fibrinolysis (42, 43) and elevated PAI-1 activity (44) have been associated with acute MI in prospective studies (45, 46). The 4G polymorphism has been associated with MI a young age in a study that examined 93 Swedish men after their first MI (41). These men were younger than 45 years of age and had genetic analysis and their PAI-1 levels measured 4 to 6 months after the index event. The frequency of the 4G allele was significantly higher among young post-infarction patients than among control subjects. PAI-1 activity was significantly higher in the control group, who were homozygous for the 4G allele.

An increase in this mutation has also been correlated with postmenopausal women with coronary artery disease (47). Pastinen *et al.* (13) analyzed 12 polymorphisms in eight genes that have been associated with coronary artery disease in a Finnish population of patients with MI and carefully matched controls. They found the 4G polymorphism of the PAI-1 gene ($P < 0.05$) and platelet PI^{A2} ($P < 0.01$) were associated with an increased risk of MI. This study was unique in the number of polymorphisms surveyed. The lack of association between MI and 10 of the 12 markers provided internal negative controls and additional strength to their conclusions. However, a number of large studies have found no association between the 4G allele and MI (48–50). A meta-analysis of the 4G/5G polymorphism reviewed a total of nine different studies with 1521 cases and 2120 controls. The 4G allele was found to confer a slight risk of MI. More importantly, patients who were carriers of the 4G allele and who were at a higher risk for MI had twice the risk for developing an MI in comparison to patients in a lower risk group who also carried a 4G allele (51). In summary, there appears to be a modest risk for MI associated with the 4G allele of PAI-1, and increased triglycerides levels may modify this genetic effect.

Factor XIII

Factor XIII stabilizes newly formed clots by crosslinking fibrin monomers to form insoluble, stable fibrin thrombi in the last step of the coagulation process (52). The risk of acute MI has been associated with high levels of plasma factor XIII activity in patients with coronary artery disease (53). Kohler and Grant (54) have found a common polymorphism (Val34 to Leu, where the Leu is present in 40%–50% of the general population) in the gene encoding the A-subunit of coagulation factor XIII that is protective against MI. After evaluating 398 patients with suspected CAD and 196 healthy controls, they found that the prevalence of FXIIIVal34Leu was significantly lower in patients with MI than in healthy controls (32% vs. 48%, $P = 0.005$). Autopsy studies are particularly useful for arterial thrombosis studies because the thrombus can be visualized. In such an autopsy study Wartiovaara *et al.* (55) found the FXIII 34Leu allele was associated with a lower risk of MI ($P = 0.009$). There are conflicting reports regarding a possible interaction of the PAI-1 4G allele and the Factor XIII 34Leu allele (54, 55).

Factor VII

Factor VII is a vitamin K-dependent glycoprotein that, once bound to tissue factor (TF), is converted to the active form, Factor VIIa. The TF:VIIa complex is able to convert Factor X to Xa, ultimately giving rise to the fibrin clot (56). The Northwick Park Heart Study made the original association between elevated Factor VII levels and MI (24). An Arg(R)353 to Gln(Q) polymorphism in FVII is an important genetic determinant for plasma FVII levels and is associated with a 20% to 25% reduction in plasma factor VII levels (57). Hunault and colleagues (58) determined that the mechanism of this reduction in factor VII levels was due to reduced secretion of factor VII and there is a genetic correlation between the R353 polymorphism of FVII and triglycerides (59).

Iacoviello *et al.* (60) genotyped 165 patients with familial MI for the polymorphisms involving R353Q and the hypervariable region 4 of the factor VII gene. A history of familial MI involved a first-degree relative with MI or stroke before age 65. After multivariate analysis that accounted for sex, age, smoking, hyperlipidemia, hypertension, and diabetes, the RR genotype of the R353Q polymorphism was associated with the highest risk followed by RQ genotype, and then by the QQ genotype. Patients with the QQ genotype had a decreased risk of MI. For the polymorphism involving the hypervariable region 4, the combined H7H5 and H6H5 were associated with the highest risk. Limitations to this study involved the small number of patients in the highest risk groups. In direct contrast to this study, Doggen *et al.* (61) performed a large study on patients with MI and found that the Arg-Arg353 genotype, despite having higher levels of factor VII, had a lower risk for MI. Other studies of patients with MI have found no association between MI and the R/Q353 polymorphism (62–64) or plasma elevations of factor VII (65). Thus, although there is a genetic basis for variations in plasma levels of factor VII, the majority of the clinical epidemiology studies do not support an association between the R/Q353 polymorphism and MI.

Factor XII

Coagulation factor XII, which is also known as Hageman factor, is activated by contact activation with negatively charged surfaces, leading to further proteolytic cleavage of the FXII molecule (66, 67). This is one of the earliest steps in the intrinsic pathway of coagulation, subsequently leading to activation of factor X and thrombin generation. Levels of activated factor XII were found to be higher in patients with a history of MI and correlate with the extent of coronary stenosis (68). Most other studies examining this issue utilized patients under stress or awaiting surgery. An important polymorphism was identified in the 5′-untranslated region of the factor XII gene. This polymorphism is a C/T at position 46, with an allele frequency of 0.8/0.2 in Caucasians and is reversed in Asians at 0.27/0.73 (69). This polymorphism appears to have a profound effect on Factor XII levels through its effects on protein translation. This polymorphism was genotyped in 266 patients with suspected coronary artery disease and no association was found with MI history or the extent of coronary artery disease. Thus, similar to factor VII, the factor XII polymorphism is associated with factor levels, but not with coronary heart disease.

Prothrombin

Prothrombin is the precursor to thrombin, which then converts fibrinogen to fibrin monomers. There is a common

polymorphism of the prothrombin gene due to a substitution of adenine for guanine at position 20,210 in the 3′-untranslated region (70). Numerous studies have shown this to be a risk factor for venous thrombosis (70–72). Croft *et al.* (73) studied 539 acute MI patients and found no association with this polymorphism. Several studies examined both venous and arterial thrombosis and identified an association between the prothrombin 20210 A/G polymorphism and venous, but not arterial, thrombosis (74–77). Only two studies have found an association between the prothrombin 20210 A/G polymorphism and MI (61, 78), but there were relatively few patients in these studies who carried the variant allele.

Factor V

Factor Va is a cofactor for the conversion of prothrombin to thrombin and factor Va is inactivated by activated protein C. Resistance to activated protein C (APCR) is the most common risk factor for venous thrombosis, and the Factor V Leiden (FVL) polymorphism is the cause of 95% of APCR (79). In a large cohort of healthy men, the incidence of factor V G1691A mutation was found to be highly correlated with venous thrombosis, but not with an increased risk of MI stroke (80). Thus, most studies have found no association for FVL as an independent risk factor for arterial thrombosis (81, 82). However, there is some intriguing evidence suggesting that the FVL polymorphism may interact with smoking to enhance the risk of MI (61, 83).

Homocysteine

Elevated homocysteine levels have been identified as an independent risk factor for MI and for mortality in patients with confirmed CAD (84, 85). A common mutation (alanine to valine at position 677) in the methylenetetrahydrofolate reductase (MTHFR) gene is associated with decreased specific MTHFR activity and elevation in homocysteine levels in the homozygous state (86). Numerous case-control studies have observed an association between the MTHFR C677T polymorphism and homocysteine levels, but not with MI or CAD (87–90). Subsequent studies have generally made similar findings, as witnessed by findings in a recent meta-analysis of 20 different studies comprising 5869 patients with cardiovascular disease and 6644 controls that concluded that the 677 C→T mutation is a major cause of mild hyperhomocysteinemia, but it does not increase cardiovascular risk (91). The possibility that this polymorphism may only exert its effect in early onset CAD (92) will need to be studied further.

Thrombomodulin

Thrombomodulin is an endothelial cell receptor that binds thrombin. The thrombin-thrombomodulin complex activates protein C, which acts as an anticoagulant by inactivating factors Va and VIIIa. At least four polymorphisms/mutations have been described in the thrombomodulin gene (93–95). The 5′ region of the thrombomodulin gene was analyzed in 104 patients with MI and was compared to 104 control subjects (94). Three distinct mutations were identified in the patient groups that were not present in the controls. Doggen *et al.* (93) examined a larger cohort of patients with MI (560 men) and identified a 127G to A mutation (Ala to Thr substitution) in 12 of the patients and seven controls. A third study identified a common C/T dimorphism predicted to cause an alanine to valine substitution that was associated with premature (<age 50) MI (95). Because these thrombomodulin polymorphisms/mutations occur with such low frequency, there have been small numbers of cases carrying the uncommon allele in these case-control studies. Much larger studies are needed to provide the necessary power to address this potentially interesting set of genetic markers.

Von Willebrand Factor

Von Willebrand factor (vWf) is required for platelet adhesion to exposed subendothelium. High levels of vWf have been associated with MI (24). Several polymorphisms in the vWf gene that are in linkage disequilibrium with each other are associated with plasma vWf levels (96). Heywood *et al.* (97) screened for different polymorphisms in the vWf promoter in patients with a history suggestive of ischemic heart disease and found a higher frequency of the uncommon allele in the cases than in age-matched controls. However, neither polymorphism was associated with vWF levels or a history of MI. These vWf polymorphisms may be potential risk factors for ischemic heart disease, but the data so far should be considered preliminary.

Platelet Polymorphisms

Platelets play a crucial role in the development of the acute ischemic coronary syndromes. Platelet GPIIb-IIIa (integrin α_{IIb} β_3) is felt to be the final common pathway in platelet aggregation and as such has been a target of several successful anti-platelet clinical trials (98–101). Because of such successes in the antiplatelet clinical trials, it becomes more than just scientific curiosity to determine whether platelet polymorphisms impact on the expression of disease. Platelet membrane adhesive glycoproteins are highly polymorphic and these polymorphisms often alter the antigenicity of the glycoprotein. Three platelet glycoproteins contain commonly occurring polymorphisms: the receptors for vWf (GPIb-IX and GPIIb-IIIa), collagen (platelet GPIa-IIa or integrin $\alpha_2\beta_1$), and fibrinogen (GPIIb-IIIa).

The PI^A Polymorphism. The most abundant platelet membrane glycoprotein is the GPIIb-IIIa complex, which is present at 80,000 copies per cell (21). Unactivated platelets are able to bind to immobilized vWf or fibrinogen through GPIIb-IIIa; activated platelets can perform this function in solution. The PL^A (or Zw or HPA-1) alloantigen was discovered over 40 years ago and more recently, the molecular basis for this polymorphism was shown to be a T

to C nucleotide substitution at position 1565 in exon 2 of the GPIIIa gene (102, 103). This results in either a leucine or a proline, respectively, at position 33 of GPIIIa. This amino acid substitution is necessary, but not sufficient, for the alloimmune response seen in certain immune thrombocytopenias. Approximately 25% of individuals of Northern European extraction have at least one PI^{A2} allele. In 1996 we reported a strong association between the PI^{A2} polymorphism and acute coronary thrombosis, particularly in patients less than 60 years of age (104). Cases were patients admitted to the Coronary Care Unit at Johns Hopkins Hospital with MI and unstable angina; controls were hospitalized patients matched for age, race, and sex, but without evidence of coronary heart disease. The PI^{A2} polymorphism was found to be twice as common in patients compared with controls, and 3.6 times higher in those patients whose event occurred prior to the age of 60.

Of the more than 40 papers that have subsequently appeared examining PI^{A2} in coronary artery disease, four general types of phenotypes have been studied: unstable coronary syndromes (such as MI and unstable angina) (13, 104–116); outcomes after coronary revascularization (114, 117–120); angiography only (105, 119, 121–123); and postmortem (124). Unfortunately, no consistent conclusions can be drawn regarding PI^{A2} risk due to the heterogeneity of the study populations and design. These studies differ by geographical origin and ethnicity, and also by many aspects of the study design. There were fundamental differences in patient accrual, age, gender, and the type of infarction. Perhaps the most important difference was the choice of control groups. In general, the control groups that were more rigorously screened for the lack of CHD and/or better matched with the cases for other risk factors had a lower prevalence of the PI^{A2} allele. This of course magnifies the difference in PI^{A2} positivity between cases and controls, and other than the study by Carter *et al.* (125), if the PI^{A2} prevalence in the control group was less than 20%, an association between PI^{A2} and acute coronary syndromes was detected.

In the coronary revascularization and angiography studies, the control groups were derived from the same starting population as the cases and were defined as those who had fewer events after revascularization or less stenosis at angiography. Although there have been fewer of these studies, a higher prevalence of PI^{A2} was observed in the cases than in the controls in every study. Autopsy studies have the obvious advantage of detecting extent of atherosclerosis, infracted myocardium, and fresh thrombus. A very informative autopsy study by Mikkelson *et al.* (124) reported that the prevalence of PI^{A2} was higher in MIs caused by thrombosis than MIs without thrombosis ($P < 0.001$ unadjusted, $P < 0.005$ adjusted). These autopsy findings are consistent with the model hypothesized by Zotz *et al.* (116) in their initial publication on PI^{A2}.

PI^{A2}-positive platelets have a lower threshold for activation than $PI^{A1,A1}$ platelets (126, 127) and these subthreshold differences by PI^{A} genotype are overcome by higher doses of agonists such as those routinely used in clinical hematology laboratories for the detection of platelet hypofunction. Aspirin inhibition of platelets also varies by PI^{A} genotype (127–129). There are conflicting reports on PI^{A} genotype differences in fibrinogen binding (130–132). To overcome the known difficulties related to interdonor platelet variability, we tested the PI^{A1} or PI^{A2} isoforms of GPIIb-IIIa in stable Chinese hamster ovary (CHO) and 293 human embryonal kidney cell lines (133). Although soluble fibrinogen binding was no different between PI^{A1} and PI^{A2} cells, significantly more PI^{A2} cells bound to immobilized fibrinogen than did PI^{A1} cells.

In summary, the Pro33 form of GPIIIa confers a prothrombotic phenotype in platelets and cell lines and a modest risk to the development of ischemic coronary syndromes. Results of angiography studies suggest PI^{A2} could be associated with atherosclerosis, but further work is needed to address this issue.

The 807 T/C Polymorphism of GPIa. Glycoprotein Ia (integrin $\alpha_2\beta_1$) is widely distributed on different cell types, including platelets, and mediates adhesion to collagen. There are at least three alleles encoding GPIa. The allele encoding the Br^a antigen is rare, but there are two alleles encoding Br^b, which are referred to as 807 T and 807 C. Platelets expressing the 807 T allele have increased surface expression of GPIa-IIa and increased platelet deposition to immobilized collagen under shear stress (134).

Polymorphisms involving this receptor have been found to be an independent risk factor for acute MI (134–139). In a 2/1 case-control study that was age and sex matched, patients homozygous for 807 T had a relative risk of 3.3 for MI when compared to controls (138). In a large study from Germany, Santoso *et al.* (139) demonstrated that inheritance of the 807 T allele of the GPIa gene represents a potent risk factor for nonfatal MI. In this study, as well as others (135), young age had a major contribution to the risk associated with 807 T. Thus, the 807 T allele of GPIa is associated with a prothrombotic platelet phenotype, and based on a small number of studies, there is reason to believe this is a risk for younger patients. As with several PI^{A2} studies, the 807 T risk was often greatest in patients of young age and smokers.

Glycoprotein Ib Polymorphism. The GPIb-IX-V receptor mediates shear stress-dependent platelet adhesion and activation via the binding of vWf to GPIbα. Three different polymorphisms of the GPIbα gene are known and several alleles have been reported as risk factors for arterial thrombosis (125, 140–143). The Ko polymorphism corresponds to a single amino acid substitution (Thr/Met145) in the α-subunit of GPIbα (144). The met145 allele has been found to be associated with acute cerebrovascular events (141, 143), acute MI (140, 142), and severity of stenosis on angiography (142). The length polymorphism of GPIbα consists of a variable number of tandem repeats (VNTR) of 39 base pairs at the amino terminus. The −5 T/C (so-called

"Kozak") polymorphism of GPIbα has been suggested to increase protein expression in one study (145), but not another (140). The Spanish case-control study did not observe an association between this polymorphism and either MI (140) or cerebrovascular disease (141). In summary, there is relatively little information on the GPIbα polymorphisms, but the available data on the met145 allele and the VNTR B/C genotypes warrant additional study.

Other Platelet Polymorphisms. Additional platelet polymorphisms are being identified at a rapid rate. There are mostly only isolated reports that suggest some of these (GPIIb, FcγRIIa, P-selectin, α2 adrenergic receptor, and TGF β) may be risk factors for arterial disease or have a prothrombotic phenotype, and these may be worthwhile avenues of investigation.

Inflammation

A major focus of atherosclerosis etiology has been the role of inflammation in the pathogenesis of coronary thrombosis. It has been shown that coronary plaque rupture is strongly associated with the severity and frequency of superficial plaque inflammation (146). Yudkin *et al.* (147) propose that interleukin-6 plays a key role in the mechanism that contributes to the development of coronary heart disease. Elevated levels of C-reactive protein (CRP) have been linked to the risk of developing an acute coronary syndrome (148–151). In one study, 1411 patients were studied after surviving MI, and CRP was found to be highest in those patients with MI and clinically manifest atherosclerosis when compared to controls. Additionally, there was also a significant association between CRP and the angiographically detected degree of coronary heart disease (149). Margaglione *et al.* (90) studied 1048 individuals without clinical evidence of atherosclerosis and investigated the relationship between CRP levels and a family history of MI (152). After measuring several proteins that included CRP, and measuring the presence of genetic polymorphisms involving the PAI-1 4G/5G allele, fibrinogen Bβ-chain G→A, and the angiotensin-converting enzyme insertion/deletion gene, they concluded that along with age and total cholesterol, raised levels of CRP and the presence of PAI-1 4G/4G allele independently identified offspring of patients with a MI.

Conclusions

Genetic variations in genes and their products affect hemostasis and thrombosis. As described in this review, in many cases there are known functional consequences of these polymorphisms (i.e., genes affecting physiology), and evidence supports a prothrombotic consequence. Table I summarizes the genetic polymorphisms we have discussed and indicates the strength of the evidence supporting a functional or clinical association. Based on our understanding of the pathophysiology of acute coronary syndromes, these functional changes provide biologic plausibility as risk factors for this phenotype (i.e., physiology affecting phenotype). The clinical utility of genetic risk factors for acute coronary syndromes (i.e., genes associated with phenotype) will be best demonstrated as we solidify the associations between these polymorphisms and arterial disease. Genotyping offers certain advantages over functional assays, which may be affected by therapies and change over time.

Polymorphisms of molecules involved in hemostasis

Table I. Summary of Genetic Polymorphisms and Their Arterial Thrombotic Risk

Gene	Polymorphism (common name)	Functional?[a]	Confidence for any arterial thrombotic risk[b]
Fibrinogen	−455G/A	++/−	+++
PAI-1	4G/5G	+++	+++
FXIII	Val 34 Leu	+/−	+
FVII	R353Q	+	+/−−
FVII	Hypervariable region 4	+/−	+/−−
FVII	−323	+/−	?
FXII	−46 C→T	+++	−
Prothrombin	20210 A	+++	−
Factor V	G1691A	+++	−
Homocysteine	MTHFR 677 C/T	+++	−
Thrombomodulin	Promoter mutations	+/−	+/−
Thrombomodulin	Ala25Thr	?	+
Thrombomodulin	Ala455Val	−	+
Glycoprotein IIIa	Leu33Pro (PI^{A2})	+++/−	++/−
Glycoprotein Ia	807T	+++	+
Glycoprotein Ib	Ko	?	+
Glycoprotein Ib	VNTR	?	+
Glycoprotein Ib	Kozak	+/−	+/−

Note. The strength of the evidence is graded from evidence against (−) to varying degrees of evidence for (+ to +++). "?" means there is insufficient evidence to render a conclusion.

[a] Functional refers to evidence for the polymorphism either causing or being associated with an altered function of the gene product that would be consistent with a prothrombotic effect.

[b] The "confidence" level is based upon numbers of studies, numbers of subjects in the studies, consistencies in results across studies, etc. It should be noted that there might be certain patient groups for whom the risk is stronger than others.

and thrombosis should be added to the list of risk factors for arterial thrombosis. These genetic variations confer only modest increases in risk. Perhaps this is not unexpected, considering the importance to the organism of maintaining blood fluidity. From an evolutionary point of view, maintenance of these risk alleles in the gene pool may have resulted from the severe consequences of bleeding from trauma and the normal bleeding of menses and childbirth. Only when these small prothrombotic effects interact with environmental effects and/or each other may the phenotype become manifest. Additional work is needed to resolve some of the inconsistencies and controversies. Further genotyping efforts from existing clinical databases will not likely improve our understanding of the issue. However, well-designed studies addressing the role of platelet in acute coronary syndromes in which the controls are matched to the cases for traditional risk factors are needed, particularly if they include women and test for treatment interactions. Genetic analyses from clinical trials are essential in order to establish interactions between these polymorphisms and response to therapy. In combination with traditional risk factors and an understanding of gene-environment interactions, these inherited markers can ultimately be used to manage patients with vascular disease through a better utilization of invasive or expensive diagnostic testing and pharmacogenetics.

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